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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/772,598 | 01/30/2001 | Timothy E. Benson | 6315.N | 2967 |

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| EXAMINER | |
|---|---|
| MAHATAN, CHANNING | |
| **ART UNIT** | **PAPER NUMBER** |
| 1631 | |

DATE MAILED: 04/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/772,598 | BENSON ET AL. | |
| | Examiner | Art Unit | |
| | Channing S Mahatan | 1631 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *23 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *35 and 38-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *39-43* is/are allowed.

6)☒ Claim(s) *35,38,and 44-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1 Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

*APPLICANTS' ARGUMENTS*

Applicants' arguments, filed 23 January 2004, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

*CLAIMS UNDER EXAMINATION*

Claims herein under examination are claims 35 and 38-66. Claims 1-34, 36, and 37 have been cancelled.

*IMPROPER INCORPORATION BY REFERENCE*

The attempt to incorporate subject matter into this application by reference to U.S. Provisonal Application No. 60/179,261 is improper because the language "preferably, the crystals have one dimension of 0.15-0.8mm, and more preferably dimensions of 0.15-0.8mm x 0.2mm x 0.05-0.1mm" is considered essential material (i.e. claimed in claims 58 and 59) and has not been indicated by Applicants as being inadvertently (unintentionally) omitted. It is acknowledged the incorporation by reference statement in the specification-as-filed states:

> "This application claims the benefit of U.S. Provisional Application Serial No. 60/179,261, filed 31 January 2000, which is incorporated herein by reference in its entirety." (page 1, lines 10-12 of the Specification)

However, M.P.E.P. § 201.06(c) entitled "Incorporation By Reference" states:

> "The incorporation by reference statement can only relied upon to permit the entering of a portion of the prior application into the continuation or divisional application when the portion of the prior

application has been inadvertently omitted from the submitted application papers in the continuation or divisional application."

Applicants' amendment, filed 23 January 2004, states on page 9:

"The specification has been amended at page 16, line 19, to add the recitation that "[p]referably, the crystals have one dimension of 0.15-0.8mm, and more preferably dimensions of 0.15-0.8mm x 0.2mm x 0.05-0.1mm. The amendment is supported, for example, by a recitation on page 3, lines 9-11, of U.S. Provisional Application Serial No. 60/179,261, which is incorporated by reference in its entirety at page 1, lines 10-12, of the present application. Specifically, the recitation on page 3, lines 9-11, of U.S. Provisional Application Serial No. 60/147,851 reads "[r]efinement of the condition yielded crystals of monoclinic morphology with a range of dimensions 0.15-0.8 x 0.2 x 0.05-0.1 mm. No new matter has been added."

and

"New claims 58-59 and 62-63 are supported by the specification at, for example, page 16, line 19 (as amended), and each of claims 38 and 35, respectively."

Such language is considered essential material as it is relied upon for support of the new claims claims 58-59 and 62-63. Absent is any indication that the above language was inadvertently omitted and an accompanying affidavit or declaration to that effect. The amendment must be accompanied by an affidavit or declaration executed by the Applicants, or a practitioner representing the Applicants, stating that the amendatory material consists of the same material incorporated by reference in the referencing application and was inadvertently omitted. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973). It should be noted the correction of "trigonal space group symmetry $P2_1$" to "monoclinic space group $P2_1$" is

understood as being inadvertent, wherein one of skill in the art would understand that $P2_1$ is a monoclinic space group symmetry.

**Claims Rejected Under 35 U.S.C. § 112 1st Paragraph**

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

*NEW MATTER*

Claims 44-66 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The introduction of the claims 44-66 in the amendment filed 08 January 2004 is is considered new matter. Applicants state the following for support of new claims 44-66:

> "Each of new claims 44, 46, 48, 50, and 52 are generally supported by the specification, and specifically supported, for example, by claim 35 and each of claims 39-43, respectively. New claims 45, 47, 49, 51, 53, and 66 are supported by the specification at, for example, page 42, lines 6-7. New claims 54 and 56 are supported by the specification at, for example, page 29, lines 22-23, and each of claims 38 and 35, respectively. New claims 55 and 57 are supported by the specification at, for example, page 15, lines 13-15. New claims 58-59 and 62-63 are supported by the specification at, for example, page 16, line 19 (as amended), and each of claims 38 and 35, respectively. New claims 60 and 64 are supported by the specification at, for example, page 29, lines 22-23. New claims 61-65 are supported by the specification at, for example, page 15, lines 13-15."

This is incorrect since there did not appear any disclosure or contemplation of the broadly encompassing crystallization conditions that would result in a crystal of *Staphylococcus aureus* NAD synthetase with, for example, a monoclinic space group symmetry $P2_1$. The specification states the following with regard to methods of crystallizing *Staphylococcus aureus* NAD synthetase:

> "The crystallization library consists of Hampton Research Crystal Screen I, Crystal Screen II, and Crystal Screen I-Lite (all available from Hampton Research, Laguna Niguel, CA) and Wizard I, Wizard II, Cryo I, and Cryo II (all available from Emerald Biostructures, Inc., Bainbridge Island, WA). NAD synthetase was screened in all conditions, with hits in Hampton Crystal Screen I-Lite/43 (15% PEG 1500), Hampton Crystal Screen 1/39 (2% PEG 400, 2.0M Ammonium Sulfate, 0.1 M Na Hepes pH 7.5), Wizard 1/41 (30% PEG-3000, Ammonium Sulfate, 0.1M Na Hepes pH 7.5, and Wizard 1/41 (30% PEG-3000, CHES pH 9.5).
>
> The largest, most easily reproducible crystals occurred in 15% PEG 1500." (page 41, lines 2-11)
>
> "Refinement of this condition showed that crystals could be obtained from 16-22% PEG 1500." (page 41, lines 20-21)
>
> "Several attempts to introduce pH buffers into this system invariably yielded poor crystals or precipitated protein. Buffer exchanging the protein solution to 100mM Tris, 5mM B-mercaptoethanol, pH 8.0 did not result in crystallization..." (page 41, line 22-25)
>
> "Capillary mounting of a crystal allowed determination that the crystal was indeed a protein and diffracted to about 3.3 Å in the X-ray facility. (pages 41-42, lines 31 and 1, respectively)
>
> "Using a washed cat wisker (a generous gift of MSHarris), seeds from prepared dilutions of the stock liquor were streaked into VDX trays containing 12-25% PEG 1500. Large crystals grew in 18%-22% PEG 1500." (page 42, lines 4-7)

The above section from the disclosure provides only specific set of crystallization conditions that would result in, for example, a crystal of *Staphylococcus aureus* NAD synthetase with the

monoclinic space group symmetry $P2_1$. The amended claims broadly encompass all crystallization conditions for crystallizing *Staphylococcus aureus* NAD synthetase with, for example, a monoclinic space group symmetry $P2_1$. The production of one crystal with particular characteristics (space group symmetry, unit cell dimensions, structure coordinates, etc) does not establish contemplation of all crystals (i.e. *Staphylococcus aureus* NAD synthetase) having some or all of the characteristics. There does not appear to be any disclosure or contemplation for the language "the crystal effectively diffracts x-rays" (i.e. claim 54), wherein the concept of effectively is not found and is not apparent (Refer to below 35 U.S.C. § 112 2nd Paragraph Rejection). Additionally, 58-59 and 60-61 are herein or further rejected, respectively, in the absence of an affidavit or declaration stating the inadvertently omission of the particular language "0.15-0.8mm x 0.2 mm x 0.05-0.1 mm". Therefore, newly added claims 44-66 are considered NEW MATTER.

**Claims Rejected Under 35 U.S.C. § 112 2nd Paragraph**

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 54-57, 60, 61, and 64 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

*VAGUE AND INDEFINITE*

Claims 54, 56, 60, 64, and all claims dependent therefrom recites the limitation "wherein the crystal effectively diffracts x-rays to a resolution of 1.5 Å to 3.0 Å /at least 2.2 Å" which is vague and indefinite. It is unclear what Applicants' regard the criteria(s)/parameter(s) of a

crystal to be such that the crystal "effectively diffracts x-rays". For example, is the crystal to be of some resolution, unit cell dimension, etc. in order for the crystal to effectively diffract x-rays? Clarification of the metes and bounds, via clearer claim language, is requested.

**Claims Rejected Under 35 U.S.C. § 103**

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claim 38 under 35 U.S.C. § 103(a) as being unpatentable over Kunsch et al. (Pub. No. US 2003/0054436) taken in view of Rizzi et al. (Proteins: Structure, Function, and Genetics. 1996, Volume 26, pages 236-238) or Sambrook et al. (Molecular Cloning: A Laboratory Manual) or Worthington (Worthington Enzyme Manual: enzymes and related biochemicals) is maintained for reasons of record.

Claims 35 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Crystal Screen (Hampton Research) taken in view of Kunsch et al. (Pub. No. US 2003/0054436). It should be noted this rejection is maintained against claim 35 and is newly applied to claim 38.

Crystal Screen™ is a complete reagent kit designed to provide rapid a screening method for the crystallization of biological molecules (i.e. proteins, etc) and allows for the determination of crystallization conditions (page 1, Column 1, lines 1-4). The Crystal Screen™ metes the limitations of the instantly claimed conditions in the method of crystallizing; for example, condition 43 indicates 30% PEG 1500. Absent from the instant claim (i.e. 35) are specific "final crystallization conditions" that would allow one to distinguish a preliminary crystal from a

specific final crystal. Absent from the instant claim (i.e. 38) are specific crystal characteristics (i.e. unit cell dimensions) that would allow one to distinguish a preliminary crystal from a specific final crystal.

Kunsch et al. discloses isolated *Staphylococcus aureus* polynucleotides and recombinant methods of producing the encoded proteins. (See pages 3-4; Summary of the Invention Section.) Table 2 at pages 42-43 discloses Contig ID Nos. 1192 and 32, as being *Staphylococcus aureus* homologs of NAD synthetase.

Thus, it would have been obvious to someone of ordinary skill in the art at the time of the invention to practice Crystal Screen™, determination of crystallization conditions for a biological molecule (i.e. protein) and obtaining a crystal (claim 38) of a biological molecule with Kunsch et al. (Pub. No. US 2003/0054436) *Staphylococcus aureus* NAD synthetase for further study and characterization of the protein and potential binding agents (i.e. drugs) (Kunsch et al. page 16, Screening Assay for Binding Agents section). Crystal Screen™ is also effective in determining the solubility of a molecule in a wide rage of precipitants and pH (page 1, Column 1, lines 4-5).

Applicants' argue: 1) Rizzi et al., Sambrook et al., and Worthington fail to teach or suggest a crystal of *Staphylococcus aureus* NAD synthetase or crystallizing Staphylococcus aureus NAD synthetase; and 2) "one of skill in the art would not equate frozen with crystalline form".

Rizzi et al., Sambrook et al., and Worthington et al. do not specifically disclose a crystal of *Staphylococcus aureus* NAD synthetase or crystallizing *Staphylococcus aureus* NAD synthetase. However, these references were cited to establish recombinant techniques for the

isolation/production of polypeptides (i.e. *Staphylococcus aureus* NAD synthetase), known to one of skill in the art at the time of the invention. One of skill in the art would therefore recognize freezing the isolated *Staphylococcus aureus* NAD synthetase polypeptide (as taught in Kunsch et al.) for storage (as taught in Rizzi et al., Sambrook et al., or Worthington et al.) resulting in a protein crystal with no further characteristics (refer to below).

Applicants' argument with respect to equating frozen with crystalline form is found unpersuasive. In fact, Applicants cited definitions, particularly the term "crystal" which is indicated to be the following:

> "A solid of regular shape and, for a given compound, characteristic angles, formed when an element or compound solidifies slowly enough, as a result either of freezing from the liquid form or of precipitating out of solution, to allow the individual molecules to take up regular positions with respect to one another."

supports the Examiner's assertion that one of ordinary skill in the art would recognize to equate the term frozen ("affected by freezing"/ "reduced to a solid state by cold"; refer to Applicants definition for the terms "frozen" and "ice", respectively) with a crystal/crystalline form; wherein absent from the above claims for the crystal and method of crystallizing are the "characteristic angles" or the "regular positions the individual molecules take up with respect to one another" (as provided for in the cited definition). Further, it should be noted the reference cited for the definition of the term "crystal" indicates its origin is from the term ice.

*ALLOWABLE CLAIMS*

Claims 39-43 are found allowable.

*EXAMINER INFORMATION*

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 C.F.R. § 1.6(d)). The CM1 Fax Center number is either (703) 872-9306.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Channing S. Mahatan whose telephone number is (571) 272-0717. The Examiner can normally be reached on M-F (8:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael P. Woodward, Ph.D., can be reached on (571) 272-0722.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instruments Examiner, Tina M. Plunkett, whose telephone number is (571) 272-0549 or to the Technical Center receptionist whose telephone number is (703) 308-0196.

Date: April 16, 2004

Examiner Initials: CSM

Marianne P. Allen

MARIANNE P. ALLEN 4/19/04
PRIMARY EXAMINER

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